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A Pharmacoreview of *Teucrium polium* L.

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ABSTRACT:
'*Teucrium polium* L.', a medicinal plant belonging to the family *Lamiaceae* is a sub-shrub and herb popularly known as 'felty germander'. *Teucrium polium* has been used for over 2000 years in traditional medicine for various types of pathological conditions, such as gastrointestinal disorders, inflammations, diabetes, rheumatism, liver disorders and stomach ailments. It also possesses hypoglycemic, hypolipidemic, antinociceptive, antioxidant and insulinotropic activities, reduces body weight and lowers high blood pressure etc. *T. polium* contains various compounds, such as iridoids, flavonoids and diterpenoids which responsible for its various activities. Various studies indicated that it possess antibacterial, antimicrobial, antifungal, antiviral, anticancer and antispasmodic activities etc. This review supports all updated information on its phytochemical and pharmacological activities, traditional uses, toxicological information and scientific approach.

Keywords: *Teucrium polium*, germander, diterpenoids, iridoids, insulinotropic, etc.

INTRODUCTION

Medicinal plants are part and parcel of human society to combat diseases, from the dawn of civilization. There exits a plethora of knowledge, information and benefits of herbal drugs in our ancient literature of Ayurvedic (traditional Indian Medicine), Siddha, Unani and Chinese medicine. According to the World Health Organization, 2003, about 80% of the population of developing countries being unable to afford pharmaceutical drugs rely on traditional medicines, mainly plant based and their active components [1, 2], to sustain their primary health care needs. Herbal medicines are in great demand in the developed as well as developing countries for primary healthcare because of their wide biological and medicinal activities, higher safety margins and lesser costs [1]. This study is to review and compile updated information on various aspects of a *Teucrium polium* L. plant used all over the world and to progress its pharmaceutical use in future.

Teucrium polium L.

'*Teucrium polium* L.' (Fig 1) is a sub-shrub and herb native to the Mediterranean region and the Middle East, which is also popularly known as 'felty germander'. Their flowers are small and ranges from pink to white, and its leaves are used in cooking and for various medicinal purposes, particularly for the treatment of stomach ailments [3, 4] and in the treatment of visceral pain, anti-nociceptive and anti-spasmodic effects. Care should be involved with use of this herb due to its known liver and kidney toxicity after prolonged use [4].

Taxonomical description

Kingdom: Plantae
Subkingdom: Tracheobionta
Superdivision: Spermatophyta
Division: Magnoliophyta
Class: Magnoliopsida
Subclass: Asteridae
Order: Lamiales
Family: Lamiaceae (alt. *Labiatae*)
Genus: Teucrium
Species: *polium* [5]

Synonyms

Teucrium capitatum L. [4], *Teucrium aureum* [5], *Teucrium expansum* [6], *Teucrium polium* L. subsp. *Vincentinum* [45]

Vernacular names

English: Polion [5], Cat thyme, hulwort, mountain germander
French: polium, pouliot de montagne, germandée tomenteuse
German: Poleigamander, Berggamander
Italian: polio, camendrio di montagna, timo bianco, polio primo
Arabic : d'aja, j'ada,
Persian: kalpooreh [4]
Other vernacular names: bu'aytaran, hashīshat tukāryān, z'atar ul-ġazāl, bizīlī el-qūt, j'adī murr [5].

Fig 1: *Teucrium polium* L. [5]

Botanical description

Teucrium polium L. *ssp .capitatum* (L) [Arcangeli] belongs to the section polium. It is the largest and most morphologically diverse section of the genus. It is a perennial shrub, 20–50 cm high, widely distributed in the hills and deserts of Mediterranean countries [7]. It is a Woody shrub at base with

dense hairy upper branches [9]. This plant is a dwarf, pubescent, aromatic shrub, possessing dense heads of white flowers [8]. The flowers are small, in clusters and range from pink to white [7]. The flowers completely lack the upper lip of the corolla [8]. Leaves are Linear or oblong, 10 mm long, 2.5-3 mm wide, with more or less strongly revolute and rarely flat margins [8, 9]. It possesses indumentum with simple and branched multicellular hairs [9]. The bruised foliage releases a pleasant aromatic scent [8]. Its Flowering period is from May to June [47].

Traditional uses

T. polium has been used for over 2000 years in traditional medicine for various types of pathological conditions, such as gastrointestinal disorders, inflammations, diabetes and rheumatism. *T. polium* was used as a traditional medicine in different countries and it was represented in the Table 1. The plant is mixed with boiled water and sugar and used as a refreshing beverage [7]. The leaves are used in cooking as a spice [9, 8] and used for various medicinal purposes especially for the treatment of stomach ailments [8]. The plant also possesses hypoglycemic and insulinotropic activities, reduces body weight and lowers high blood pressure and has hypolipidemic, antinociceptive and antioxidant properties [7, 8]. *T. polium* was also used by people to treat liver disorders, diabetes, stomach ailments and inflammations. Its extract was also known to induce hypoglycemic, antipyretic and intestinal motility activities and alleviates cough caused by common cold, decrease the bronchitis symptoms and duration. In addition, it is used to reduce high cholesterol [10]. *Teucrium polium* were also prescribed to alleviate diseases including tumor reduction, ulceration, diabetes, kidney stones, inflammations, rheumatism, and muscle relaxation [36]. Recently, the evaluation of cytotoxic effects of an ethanol extract of *T. polium*, on four cell lines, showed that the extract suppressed the growth of all tested cell lines [7].

PHYTOCHEMICAL CONSTITUENTS

Phytochemical investigations have shown that *T. polium* contains various compounds, such as iridoids, flavonoids and diterpenoids [7].

Essential oil

In aerial parts, Carvacrol (10.1%), caryophyllene (9.8%), torreyol (7.6%) and caryophyllene oxide (5.0%) were the main compounds of *T. polium* among 150 compounds identified. As in the other oils studied, sesquiterpenes constituted the main fraction and accounted for 55.8% of the total oil with a prevalence of sesquiterpene hydrocarbons (32.7%) over oxygen-containing sesquiterpenes (23.1%). Among the 26 sesquiterpene hydrocarbons, caryophyllene (9.8%), α-humulene (3.8%), germacrene D (3.1%), α–amorphene (3.0%) and δ–cadinene (2.9%) were the most abundant. In the other fraction, torreyol (7.6%) and caryophyllene oxide (5.0%) prevailed [7, 58]. Monoterpenes contributed 14.8% of the oil, with a predominance of oxygen-containing monoterpenes (13.6%), particularly cis-verbenone (3.7%) and cis-verbenol (2.1%). Phenols (11.6%) were represented almost entirely by carvacrol (10.1%) [7]. Among the 28 compounds identified, the main constituents of the essential oil from leaves of young branches obtained by hydrodistillation method were α-pinene (12.52%), linalool (10.63%), Caryophyllene oxide (9.69%), β-pinene (7.09%) and β-caryophyllene (6.98%) which all were analyzed and identified by gas chromatography and mass spectrometry [8]. Germacrene B, the main compound of the essential oil has been detected in *T. polium* in small amounts [44]. There is a great polymorphism in the volatile oils of *T. capitatum*, probably due to genetic factors, the plants collected at the type of developmental stage and in very close localities with similar ecological features [7].

Leaves and stems

T*eucrium* species contains neo-clerodane-diterpenoids and flavonoids (Fig 2) [9, 17]. It is reported that leaves and stems of the *T. polium* contains flavanoids such as cirsiliol and cirsimaritin *etc*. *T. polium* contains apigenin 5-galloylglucoside as its major component and apigenin 7-glucoside, vicenin-2 and luteolin 7-glucoside in smaller amounts. All the flavonoids detected were flavones with only one methylated flavone cirsimeritin (5, 4'-dihydroxy-6.7-dimethoxyflavone) [9]. Seven new neo-clerodanes 1–7 (teupolins VI–XII) and eleven known compounds 8–18 (Fig 3) were isolated and characterized from a polar extract of *T. polium* leaves. Compound 1, named as teupolin VI, was obtained as white amorphous powder. The structures of these compounds were elucidated by 1D and 2D NMR experiments and by mass spectrometry analysis [12]. Aerial parts of the plant's methanol extract yielded four major flavonoids. Compounds were identified as rutin, apigenin, 3',6 dimethoxy apigenin and 4',7 dimethoxy apigenin [48].

Roots

Abeo-Abietanes, (Fig 4) isolated and characterized from ethyl acetate root extract of *Teucrium polium* L., reported to have hypolipidemic, hypoglycemic, anti-nociceptive and anti-inflammatory effects [13]. Teuvincenone H (6), a rearranged abietane diterpenoid previously found in the roots of *Teucrium polium* L. subsp. *expansum* [45]

PHARMACOLOGICAL ACTIVITIES

Antimicrobial activity

The antibacterial activity of methanolic extracts of *Teucrium polium* were tested against five bacteria, *E. coli* MC4100, *Bacillus subtilis*, *Pseudomonas diminutus*, *Paracoccus paratrophus* and *Micrococcus luteus*. Extracts of *T. polium* showed significant growth inhibition against *Bacillus subtilis*, *Micrococcus luteus* and *Paracoccus paratrophus*. The antibacterial activity of *T. polium* extracts can be attributed to its contents in flavonoids. Reports have shown that methanolic extract of the plant inhibited the growth of *Staphylococcus aureus*, *Salmonella typhi* with a MIC of 40 mg/mL, *Bordetella bronchiseptica*, and *Bacillus anthracis* with a MIC of 10 mg/mL. This concentration of 10 mg/mL also represents the minimal bactericidal concentration (MBC) against *Bacillus anthracis* [14].

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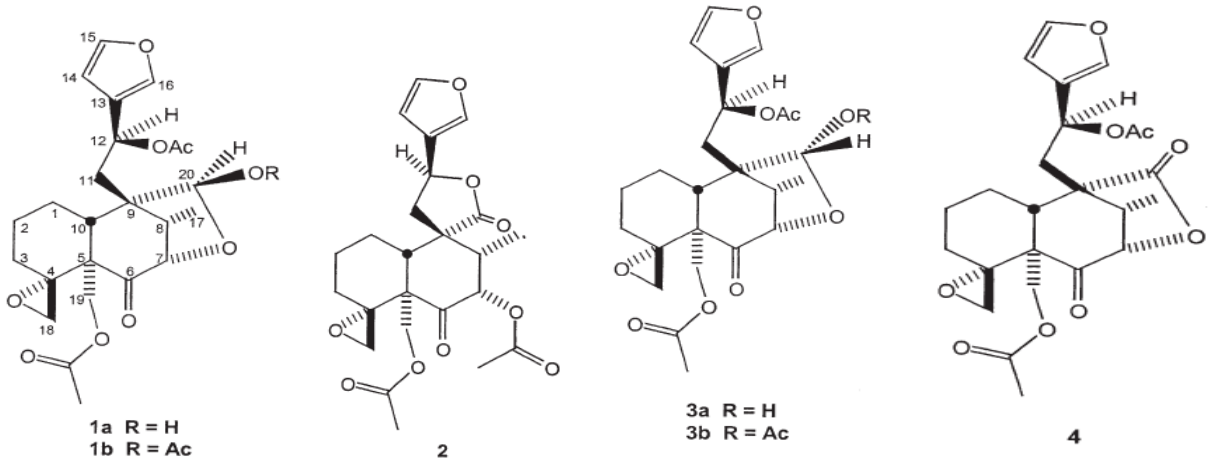
Table 1:Traditional uses of *Teucrium polium* L.

Type of medicine	Parts used	Medicinal use	Reference
Indian	Aerial parts	as a mode of infusion for the treatment of spasm, flatulence, necrosis, diabetes and kidney stones, anti-inflammatory, Anti carminative and antiemetic activities	[11], [13]
Persian	Leaves, stems, roots	Antihypertensive, anti-bacterial, carminative, anti-nociceptive, anti-inflammatory, anti-diarrhea, anti-diabetes and anticonvulsant agent.	[4]
Iranian	Whole plants	Anticonvulsant, antispasmodic , antibacterial, antiulcer, hypotensive, anorexic and antipyretic activities, diuretic and diaphoretic properties	[8]
Arabic	Leaves and stems	Kidney, liver diseases, diabetes, stomach and intestinal pain and inflammation	[47]

Phytochemical constituents of *Teucrium polium* L.



Auropolin Capitatin

Fig 2: Flavanoids from the aerial parts of *Teucrium polium* L. [17]

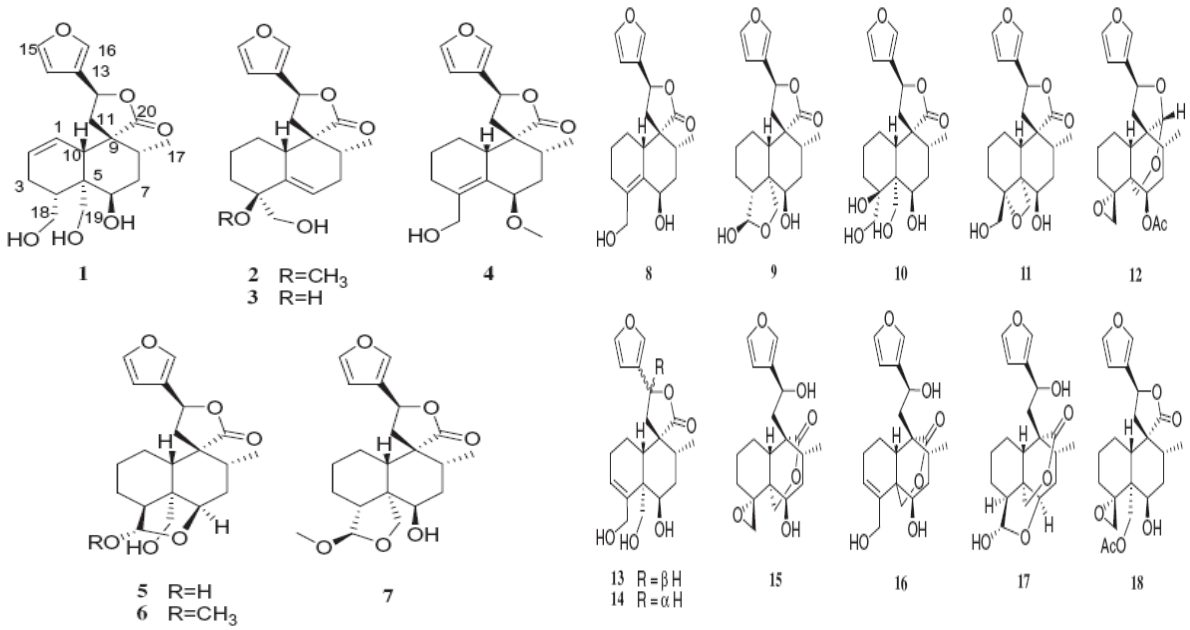


Fig 3: Teupolins VI-XII and Neo-clerodane diterpenoids 8-18 from leaves and stems of *Teucrium polium* L. [12]

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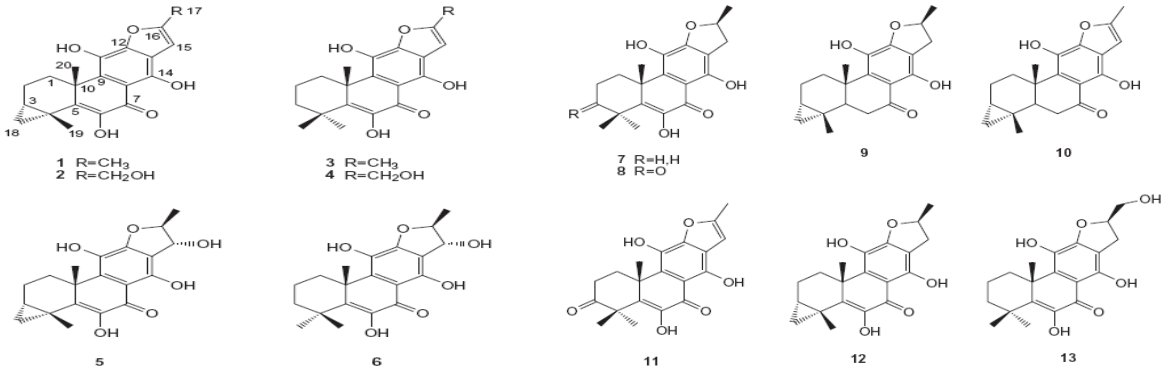

Teuvincenone H

Fig 4: Abeo-abietanes from roots of *Teucrium polium* L. [13, 45]

Antimicrobial activity of the chloroform and acetone extracts (50-250µg) of *T. polium* were also examined by means of disc-diffusion methods with eleven microbial species such as *Bacillus megaterium, Proteus vulgaris, Listeria monocytogenes, Bacillus cereus, Staphylococcus aureus, Bacillus brevis, Klebsiella pneumoniae, Micrococcus luteus, Pseudomonas aeruginosa, Escherichia coli* and *Mycobacterium smegmatis* and four fungal species *Penicillum frequentans, Fusarium equiseti, Aspergillus candidus* and *Byssochlamys fulves*. The both extracts were effective in inhibiting the growth of the organisms except for *Escherichia coli*. Antifungal activity of each of above extracts is lower than antimicrobial activity relatively [57].

Antiviral activity

Water distilled essential oils isolated from the aerial parts of *T. polium* species significantly reduced CMV infections. The investigated essential oils were proved to reduce lesion number in the local host *Chenopodium quinoa* Wild. Infected with Cucumber Mosaic Virus (CMV) it is very effective in reducing local lesion number (41.4%), when compared with other species of *Teucrium* sp. The common feature of all investigated oils is the presence of *β*-caryophyllene and germacrene D in relatively high percentages. Reports were confirmed that *β*-caryophyllene is effective in reducing CMV infection. The percentage of *β*-caryophyllene in the oil correlates with antiviral activity of the oil while the investigated oils from *Teucrium* species were also rich in sesquiterpenes. Reports have shown that *T. polium* showed significantly stronger antiviral activity against CMV than essential oil of other plants such as *S.montana etc*. Literature studies deals that sesquiterpene-rich essential oils are potent inhibitors of CMV infection and natural substances with possible role in the control of plant virus diseases [15].

Genotoxicity

Ethanolic and aqueous of *Teucrium polium* extracts significantly increased ($P < 0.005$) the level of chromosomal aberrations and the percentages of micronucleated cells compared to the DMSO control [16, 54]. Treatment with ethanol extracts in combination with MNNG significantly ($P < 0.05$) reduced chromosomal aberrations in all treatment types and led to a significant reduction ($P < 0.05$) of micronucleus formation upon pre-treatment [16] while the aqueous extract itself induces significant increases of chromosomal aberrations, which in combination with MNNG cause a higher yield of damage. Pre-treatment does not have a comparable effect which eventually is due to the induction of drug metabolizing enzymes shifting the metabolism to non-reactive metabolites. In addition, post-treatment also resulted in the recovery from MNNG damage [54]. Results indicate that both the extracts exhibited a slight but significant genotoxic potential.

Antifeedant activity

Aerial parts of this plant were found to have antifeedant activity against the final stadium larvae of *Spodoptera littoralis*. The neoclerodane compounds isolated from extract were tested at a range of concentration from 1 to 1000 ppm. A comparison of the antifeedant activity against *S. littoralis* of the synthetic compound acetyl-auropolin with the lack of activity of auropolin shows the importance of the esterification of the hydroxy group at C-20. Compound 4 with a lactone at C-20 isolated from the aerial parts showed antifeedant activity at higher concentration and an FI_{50} of 230 ppm. Capitatin compound showed a significant activity at 100 ppm but the activity was not dose-dependent. Other reports on capitatin at 100 ppm showed a Feeding Index (mean (s.e.m.)) of 45 (3.4) and 26 (8.4) against *S. littoralis* and *S. frugiperda*, respectively [17].

Antitumor activity

The essential oils of the extract were evaluated for their in vitro cytotoxic properties on three human cancer cell lines: colon adenocarcinoma CACO-2, large lung carcinoma COR-L23 and amelanotic melanoma C32 by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The most antiproliferative oils were those from T. polium ssp. Capitatum on CACO-2 cell lines, with IC_{50} values of 52.7µg/ml while significant activity was exerted by *T. polium ssp. capitatum* oil on melanoma (IC_{50} value of 91.2µg/ml). Some caffeic acid-containing phenylpropanoid glycosides extracted from *T. polium* were previously shown to have cytotoxic and cytostatic activity against several kinds of cancer cells, while the ethanol extract of the same plant suppressed the growth of four tested cell lines effectively [7].

Methanolic extract of *Teucrium Polium* (Me-TP) were also evaluated to know its promoting effect on cytotoxic and apoptotic activity of anticancer drugs of vinblastine, vincristine and doxorubicin *in vitro*. Skmel-3, Saos-2, SW480, MCF-7, KB, EJ and A431 cell lines were used to determine the Cytotoxicity by MTT assay and colony formation assay. The vincristine/Me-TP, vinblastine/Me-TP and doxorubicin/Me-TP combinations showed a strong synergistic effect in the cell growth inhibition (0.13<CI<0.36). Similar results were observed by colony formation assay. Furthermore, the combinations of vincristine/Me-TP and vinblastine/Me-TP resulted in a massive apoptosis (>80%) compared to effect of individual drugs (0-3%). At the additional experiments, Me-TP reduced marginally to significantly the cytotoxic effects of vincristine and vinblastine toward the human fibroblasts ($p<0.05$ to 0.001). Reports reveal that Me-TP has the potential to be used as an effective and safe chemosensitizer agent for cancer therapy [18].

Analgesic and Antinociceptive activity

In traditional Persian medicine it was used as antipyretic and antinociceptive agents [4]. The analgesic effect of *Teucrium polium* leaf extract was studied in the streptozotocin (STZ)-induced diabetic rats. The extract dose of 100 and 200 mg/kg per day was administered intraperitoneally for a period of 2 weeks. It was found out that *Teucrium polium* treated diabetic rats exhibited a lower nociceptive score as compared to untreated diabetics. The result reveals the therapeutic potential of *Teucrium polium* extract for the treatment of diabetic hyperalgesia [19]. The effect of the total extract and essential oil of *Teucrium polium* L. was also studied on writhing test, a visceral pain model in mice. The total extract and essential oil were administered intraperitoneally 30 min before acetic acid 0.6% injection. Total extract in doses (mg/kg) of 150, 225, 300 induced reduction in writhing response as compared to control with the $ED_{(50)}$ 67.92 mg/kg. The essential oil in doses (mg/kg) of 9.37, 18.75, 37.5, 75 and 150 induced significant reduction in writhing response when compared to control with the $ED_{(50)}$ of 29.41(mg/kg). In order to ensure the importance of essence in production of visceral antinociception, the extract free from essential oil was prepared and injected into mice at a dose of 225(mg/kg) (the most effective dose of the extract) which in comparison to total extract, the antinociception reduced from 65.44 to 49.85% ($P<0.001$). It is concluded that essential oil is responsible for analgesic properties of *T. polium*. This study confirms the antivisceral pain properties of *T. polium* comparable to those of hyoscine and indomethacin [20].

Anti-inflammatory activity

The ethanolic extract of *T. polium*, at a dose of 500 mg/kg body weight, produced significant inhibition of carrageenan-induced inflammation and cotton-pellet granuloma. Biochemical studies showed a significant decrease in glucose level. The presence of flavonoids and sterols might be responsible for the anti-inflammatory activity of this plant [7, 21]. The essential oil of the same species was found to be responsible for analgesic properties of the plant when studied by a writhing test, a visceral pain model in mice. Reports showed a significant anti-inflammatory effect [7]. The anti-inflammatory activity of essential oils from *Teucrium spp*. was also studied in vitro by analyzing their inhibitory effects on chemical mediators released from macrophages. The beneficial effect of essential oils from *Teucrium spp*. on the inhibition of production of inflammatory mediators in macrophages may be mediated by oxidative degradation of products of phagocytes, such as O^{2-} and HOCl. Incubation of RAW 264.7 cells with essential oils from *Teucrium polium spp*. induced a significant inhibitory effect on the LPS-induced nitrite production, with IC_{50} values of 16.5 and 29.4 μg/ml which is lower than those of the positive control, indomethacin. The highest anti-inflammatory activities of *T. polium ssp. Capitatum* and other species were probably due to their major components, caryophyllene and carvacrol, which showed anti-inflammatory activity in previous studies. Essential oils from *Teucrium spp*. did not showed any cytotoxicity at concentrations of 10 –100 μg/ml [7].

In another study, the effect of acute and chronic perineural treatment of the rat saphenous nerve with *Teucrium polium* L. extract on the conduction property of primary afferent nerve fibers and carrageenan-induced skin inflammation were studied. Direct application of 2.0% *T. polium* extract to the nerve trunk caused immediate complete inhibition of compound action potentials (CAPs) of all types of primary afferent nerve fibers. These results indicate that *T. polium* contains one or more potent non-selective neurotoxic agents with anti-inflammatory activity [61].

Hypolipidemic activity

The extracts of eight plants used in Arab traditional medicine in Israel and the Palestinian area to treat liver disease, jaundice or diabetes can suppress Fe^{2+}- induced lipid peroxidation and are not toxic. Of these extracts, *Teucrium polium* and *Pistacia lentiscus* were the most effective in suppressing Fe^{2+}-induced lipid peroxidation. Interestingly, the extract prepared from *Teucrium polium* is the only one used to treat both liver disease and diabetes [47]. The aqueous extract of aerial parts of *Teucrium polium*, given intraperitoneally at doses from 50 to 150 mg/kg for 10 days, reduced significantly the serum levels of cholesterol and triglycerides in hyperlipidemic rats. Treatment of hyperlipidemic rats with aqueous extract of *T. polium* aerial parts induced a significant ($P>0.05$) and dose-dependent reduction of total serum cholesterol as compared with control; also a dose-dependent reduction in triglyceride levels in treatment groups was observed, even if the difference was significant only at 100 and 150 mg/kg doses. *T. polium* water extract caused a 29- 46% reduction in total cholesterol and up to a 34% reduction in serum triglyceride in this animal model of hyperlipidemia. It has been reported that some flavonoids have antihyperlipidemic properties, while some terpenoids could inhibit lipid peroxidation [22].

Anti ulcer activity

Aqueous extract of *Teucrium polium* was broadly used in folk medicine for treatment of gastric ulcer in Iraq and some Arab countries. The induction of gastric ulcer was done in starved rats by reserpine (20 mg/kg i.p.) or by stress. *T. polium* as a crude extract dose of about 150 mg/kg i.p. produced 50% healing of ulcers while the oral administration of the extract produced 85% healing activity of the ulcers. These results were compared with proglumide and with saline in control animals [24]. In other study where induction of gastric ulcer was done by indomethacin (25

mg/kg/stat).After 4 weeks of treatment with *T. polium*, more re-epithelialization, proliferation, mucosal hyperplasia, migration of the gastric epithelial cells, and decrease in inflammatory cells were observed. *T. polium* reduced the ulcer indices by >50% after one week, >80% after 2 weeks, and >90% after 4 weeks. The healing effect of *T. polium* may be due to antioxidant activity along with the ability to modulate the mucin secretion, prostaglandin synthesis, and epidermal growth factor receptor expression. Results prove that along with the non-toxicity properties of *T. polium*, it can be used as a promising anti-ulcer compound [25].

Anti larvicidal activity

The essential oil from *Teucrium polium* showed an adverse effect on larval instars of *Musca domestica*. The essential oil was blended with a diet at a concentration that produced 50% mortality of subjected insects (LC_{50}) (80 ppm). The essential oil caused a reduction of 61.5% in tryptic activity. Significant 69% and 79% reductions were also observed in cathepsin L and B activities, respectively. Carbohydrase activities of α–amylase, α-glucosidase and β-glucosidase were detected in larval midgut extract. All assayed carbohydrases were affected by the essential oil. The most notable impact, a 93% reduction, was observed in α-amylase and decreases of 69.5% and 42% were obtained in α-glucosidase and β-glucosidase activity, respectively. This study indicated that the larvicidal effect of the essential oil from *Teucrium polium* may be due to its detrimental effects on digestive enzymes. It seems that the detrimental effect of the oil can be due to both the inhibitory nature of the oil and the destruction of the midgut epithelium [26].

Anti-convulsant activity

The protective effects of ethanolic, aqueous extracts and related fractions of *T. polium* on seizures induced by pentylenetetrazole (PTZ) and maximal electroshock stimulation (MES) were determined. It was found that aqueous extract (ED_{50} = 22.4 mg/kg body weight) and related *n*-butanol fraction (ED_{50} = 12.6 mg/kg body weight) have antiseizure effects compared to control groups. There was no difference between preventing of PTZ-induced death and MES-induced hind limb tonic extension (HLTE) in ethanolic extract comparing to control groups. Results revealed that the amount of flavonoid quantity present in aqueous extract is higher than that of ethanolic extract. These data also showed that flavonoid rich extracts are more potent than other fractions in showing antiseizure effects. *T. polium* aqueous extract and fractions of it are able to produce potent anticonvulsant activity in both MES and PTZ seizures [27].

Antispasmodic activity

Aqueous extract of the aerial parts of the *Teucrium polium* exhibited the antispasmodic activity. The extract (47- 470 mg/l) induced significant relaxation in isolated guinea pig ileum precontracted with acetylcholine. The relaxation induced by the extract was concentration dependent. The final concentration of the extract (470 mg/l) produced 93.5% inhibition of acetylcholine-induced contraction. The extract caused a non-parallel rightward shift in acetylcholine concentration response curve and the maximum response to acetylcholine was not achieved in the presence of extract. Therefore, the mode of inhibitory effect of aqueous extract on acetylcholine concentration response seems to be non-competitive antagonism at muscarinic receptor which attenuates the maximum response, to acetylcholine. These results shows that *Teucrium polium* aqueous extract have anti-spasmodic effects and may have some clinical benefits for gastrointestinal disorders [28].

Anti amnesic activity

The ethanol extracts of aerial parts of the plants was evaluated for anti amnesic activity by step through passive avoidance test apparatus in mice at 100, 200, and 400mg kg^{-1} doses. Latency time was taken as the main parameter to measure memory-enhancing effects of the extracts. Results revealed that the ethanol extracts of *Teucrium polium* showed a memory-enhancing effect of 55.4 and 61.6% at the tested doses 200 and 400mg kg^{-1}, respectively and exerted a dose-dependent effect. *Teucrium polium* could be beneficial in the treatment of cognitive impairment on account of their multifarious activities related to Alzheimer's disease [29].

Antipyretic activity

The antipyretic and antibacterial activities of the ethanolic extract of the flowering tops of *Teucrium polium* L. were been studied. The extract was found to be effective against both yeast and carrageenin pyrexia in rats. It also exhibited a marked antibacterial action against both gram positive and gram negative organisms and was found to be non toxic in acute studies [31].

Antilisterial activity

Ethanol extracts from six species representing six different families, used in traditional medicine in Turkey were evaluated for their antilisterial activities. Antilisterial activity was tested against four different *Listeria* isolates such as *L.monocytogenes*, *L.ivanovii*, *L. innocua*, and *L.murrayi* by the agar diffusion method and the macrodilution method. *Teucrium polium* L. showed antilisterial activity against *L. monocytogenes* [32].

Antiamoebic activity

Amoebic keratitis is difficult to treat without total efficacy in some patients because of cysts, which are less susceptible than trophozoites to the usual treatments [35]. Morbidity and mortality due to enteric protozoan infections remain an important health problem worldwide mainly in population from developing countries. Water extracts of plant species exhibited a dose dependent antiamoebic activity against *E. histolytica* trophozoites. *T. polium* water extract dose of about 32 mg/ml eliminated all the trophozoites after the 24th hour [23]. Methanol extracts of plant species exhibited a dose dependent antiamoebic activity against *Acanthamoeba castellani trophozoites*. In the presence of methanolic extracts, (ranging from 1.0 to 32.0 mg/ml) numbers of the viable *Acanthamoeba castellani trophozoites* and cysts were decreased during the experimental process. The extracts showed time and dose-dependent amoebicidal action on the trophozoites and cysts. Within 48th hour of treatment with methanolic extract of *T. polium*, no viable trophozoites were

observed at 32 mg/ml concentration. But cysts were found more resistant to the extracts than the trophozoites [35].

Antibrucella activity

Brucellosis, a zoonosis caused by four species of brucella, has a high morbidity. *Brucella melitensis* is the main causative agent of brucellosis in both human and small ruminants. As an alternative to conventional antibiotics, medicinal plants are valuable resources for new agents against antibiotic-resistant strains. Anti-brucella activities of ethanolic and methanolic extracts of *Teucrium polium* were assessed along with other 7 plants. The activity against a resistant *Br. Melitensis* strain was determined by disc diffusion method at various concentrations from 50–400 mg/ml. Antibiotic discs were also used as a control. *Teucrium polium*, showed anti-brucella activity. Ethanolic extract of *Teucrium polium* exhibited an inhibitory effect at all concentrations except at 50 mg/ml [33].

Hepatoprotective effect

Hepatoprotective activity of the ethyl acetate extract of *Teucrium polium* L. was investigated using rats with CCl_4 - induced liver damage .Lipid peroxidation in CCl_4-intoxicated rats was evidenced by a marked increment in the levels of thiobarbituric acid reactive substances. Histopatological examinations of the liver were undertaken to monitor the liver status. Silymarin was used as a standard to compare the hepatoprotective activity of the extract. Some biochemical parameters in groups treated with the *Teucrium polium* extract at a dose of 25 mg kg^{-1}, showed significantly different values than that of the CCl_4-treated group. The liver biopsy of all experimental rat groups treated with the ethyl acetate extract of *Teucrium polium* showed significant restoration of the normal histomorphological pattern of liver cells. The study substantiates the potential hepatoprotective activity of the ethyl acetate extract of *Teucrium polium* L. [30]. *Teucrium polium* is used in Arab traditional medicine to treat liver diseases. Glutathione is an important intracellular antioxidant, and intrahepatic glutathione levels are depleted in liver diseases. Aqueous extracts of *T. polium* maintains intracellular glutathione levels by augmenting glutathione peroxidase and glutathione reductase activity in cultured hepatocytes. The effects of increasing concentrations (0.01–1mg/mL) of aqueous extract of *T. polium* were assessed in cultured HepG2 cells. At concentrations of 0.375 mg/mL and 0.5mg/mL, the extract increased the intracellular levels of total and reduced glutathione and had no effect on the intracellular amounts of oxidized glutathione. The extract doesn't show any effect on glutathione peroxidase and glutathione reductase activities. These data indicate that the mechanism of the hepatoprotective action of aqueous extracts of *T. polium* may be, in part, due to augmenting intracellular glutathione levels [34].

Invitro antiacetylcholinesterase activity

Cholinergic neurons in the central cholinergic system (CCS) possess an important function in the process of learning and memory, which is influenced by drugs effective in this system. Dysfunction of the CCS is also associated with the pathogenesis of Alzheimer's disease (AD). Therefore, the measurement of scopolamine-induced amnesia has been extensively used as an experimental model to screen pure molecules or extracts with possible efficiency against AD. The hydroalcoholic extracts of *Teucrium polium*, were tested for their *invitro* AChE inhibitory effect at 0.25, 0.50, 1.0, and 2.0$mgml^{-1}$ concentrations. The extracts showed a mild inhibition as compared to galanthamine. The most active one was found to be *Teucrium polium* having IC_{50} value at 0.55 mg/ml [29].

Invivo hypoglycemic activity

"*Teucrium polium* L" (TP) has been long recommended in Iranian folk medicine for its antidiabetic activities [56]. The claimed hypoglycemic activities of *Teucrium polium* L were evaluated using normoglycemic and alloxan induced hyperglycemic rabbits by intranasal administration of the plant crude extracts (10%) in a vehicle containing 5% (w/w) Pluronic F127. No significant difference was observed between the extract treated and non-treated control animals receiving only water [38]. The amounts of *Teucrium polium* extract were calculated for each rabbit on body weight basis 82 mg/kg which was equivalent to 2g/kg of dried plant and prepared by dissolving in 10 ml of water. Also administration of 82 mg/kg *Teucrium polium* did not cause any reduction in blood glucose levels in both STZ-treated and untreated rabbits. Results suggest that treatment of this plant extract may not be useful in preventing the increase of glucose level in diabetic rabbits [39].

The aqueous extract of *Teucrium polium* has long being used in Iran as a hypoglycemic aid without any knowledge about its probable side effects and mode of action. The crude extract (0.5 g plant powder per kg body weight) was administered orally to a group of streptozotocin induced diabetic rats for six consecutive weeks. A significant decrease (64%) in blood glucose concentration was observed in the treated animals compared to the untreated diabetic rats, without any measurable effects on the major biochemical factors. In addition, the crude extract significantly enhanced the blood insulin level by almost 160% compared to the untreated diabetic rats. The insulinotropic property of the *Teucrium polium* extract was further assessed by an in vitro investigation using isolated pancreatic rat islets. Their findings indicated that *Teucrium polium* crude extract is able to enhance insulin secretion by almost 135% after a single dose of plant extract (equivalent to 0.1 mg plant leaf powder per mL of the culture medium) at high glucose concentration (16 mmol/L). Meanwhile, the time pattern of insulin secretion was not affected by the plant extract compared to the untreated islets. These data clearly show that the plant extract, probably without metabolic transformation, is able to reduce high blood glucose levels through enhancing insulin secretion by the pancreas [37].

Other studies such as *in situ* perfused pancreas method revealed that methanolic extract of aerial parts stimulates the basal insulin secretion, and is also able to potentiate glucose stimulated release of insulin from *in situ* isolated perfused rat pancreas. Aqueous extract of TP does not have any effect on pancreas insulin secretion. Therefore, probably it reduces blood glucose via mechanisms such as enhancement of peripheral metabolism of glucose rather than an increase in insulin release. It might be due to the presence of the component 5-hydroxy-4',7-dimethoxyflavone (apigenin-4',7-dimethylether) in methanol fraction. The insulinotropic properties of TP extracts can be attributed to the presence of

apigenin existing only in Methanol Extract, but not in aqueous extract and fractions [56].

Invitro protein glycoxidation effect

The involvement of free radicals and oxidative reactions in protein glycoxidation processes, compounds with antioxidant activities have been tested in order to reduce or to stop glycoxidation [41]. The role of oxidative protein damages in the pathophysiology of human diseases is currently a topic of considerable interest as oxidised proteins has been implicated in a wide spectrum of clinical disorders. The protective effects of four Iranian medicinal plants against oxidative damages induced by a free radical generating system were studied. Thus, the suppressive effect of each plant extract on protein oxidation could be attributed to its antioxidant activity, in addition to the suppression of lipid peroxidation. *T. polium* is more effective than the other plant extracts in protecting against the oxidative damage caused by the Fe^{2+}/ascorbate system. The antioxidant activities of *Teucrium* against metal – catalyzed protein oxidation were evaluated by pro-oxidant model (Fe^{2+}/ascorbate) in rat liver homogenates. The addition of Fe^{2+}/ascorbate to the liver homogenate significantly increased the extent of protein oxidation, such as protein carbonyl (PCO) formation and loss of protein-bound sulphydryl (P-SH) groups. The rates of reactive oxygen species (ROS) formation and lipid peroxidation (LPO) were also increased. The plant extracts showed inhibitory effects against PCO formation, P-SH oxidation, ROS formation and LPO to varying degrees. The protective effects of each plant extract could be due to its polyphenolic content. In that respect, the *T. polium* extract with highest polyphenolic content has more antioxidant activity against protein oxidation. In the presence of each of the plant ethanol extracts at two different concentrations of 25 and 50μg/ml, the extent of PCO was significantly reduced [40].

Ethyl acetate fraction of *T. polium* also possessed the highest antioxidant activity and total phenolic and flavonoid contents. The inhibitory effect of Ethyl acetate fraction on bovine serum albumin (BSA) glycoxidation measured in terms of advanced glycation end products (AGEs) and pentosidine formation as well as protein oxidation markers including protein carbonyl formation (PCO) and loss of protein thiols. Reducing sugars such as ribose and glucose increase fluorescence intensity of glycated BSA in terms of total AGEs and pentosidine during 21 day of exposure. Moreover, sugars cause more PCO formation and also oxidize thiol groups more in glycated than in native BSA. EtOAc extract at different concentrations (10–100 μg/ml) has significantly quenched the fluorescence intensity of glycated BSA. The inhibitory effect of Ethyl acetate extract in preventing oxidative protein damages including effect on PCO formation and thiol oxidation are believed to form under the glycoxidation process. These results clearly demonstrate that, the Ethyl acetate fraction, owning to its antioxidant content, is capable of suppressing the formation of AGEs and protein oxidation *in vitro* [41].

Antioxidant activity

Oxidative stress is known responsible in pathogenesis of various diseases like inflammatory bowel disease, diabetes, hyperlipidema, hepatothoxicity, osteoporosis and exposure to xenobiotics. In most of these conditions, use of antioxidants has been beneficial in ameliorating or even reversing the disease. Medicinal plants with antioxidative properties may be useful for the prevention of atherosclerosis and cardiovascular diseases by reducing formation of oxidized lipids and altering their metabolism [60]. The aerial parts of the plant extracted with different solvents were evaluated for antioxidant activity by DPPH assay. The antioxidant flavonoids were separated from the methanol extract and were identified as rutin, apigenin, 3',6-dimethoxy apigenin and 4',7-dimethoxy apigenin; their IC_{50} values in the DPPH assay were found to be 23.7±1.9μg/ml, 30.3±2.1μg/ml, 31.5±3.4μg/ml and 37.4±3.4μg/ml, respectively. The DPPH assay IC_{50} value for the methanol extract was found to be 20.1±1.7μg/ml; this value is similar to the IC_{50} value of the synthetic antioxidant, butylated hydroxytoluene (18.3±1.9μg/ml)[2, 48]. The ethanol extract prepared from *T. Polium* exhibited the same antioxidant activity as α-tocopherol [2]. The total antioxidant and the others antioxidant activities of *T.* polium are increased with increasing amount of sample (50-250μg). However, the chloroform extract of *T. polium* exhibited stronger antioxidant activity than the acetone extract. In the both extracts, the highest total antioxidant activity, DPPH radical scavenging activity, metal chelating activity and total phenolic compounds were found in chloroform extract of *T. Polium* [57].

The antioxidant activity of the ethanol extract of the whole plant by ABTS method showed significant activity at 15.00 mmol TEAC/g dry weight and compared with α-tocopherol analogue, Trolox [49]. The aqueous extract of *T. polium* can effectively inhibit oxidative processes and has substantial antioxidant activity *in vitro* [2]. An aqueous extract prepared from the aerial components of *T. polium*, was very effective in suppressing iron-induced lipid peroxidation in rat liver homogenates and inhibited oxidation of β-carotene, and tended to increase intracellular GSH levels resulting in a decrease in the GSSG/GSH ratio. IC_{50} of the extract to inhibit Fe^{2+}-induced lipid peroxidation in rat liver homogenates was 16 ± 2 μg ml^{-1}. This IC_{50} value is considerably lower than concentrations at which the extract inhibits the activity of Xanthine Oxidase and similar to the concentration at which the extract inhibited Fe^{2+}-induced lipid peroxidation in rat liver homogenates. In deoxyribose degradation assay, the extract was capable of scavenging $OH^{\bullet}$ and binding free iron. The IC_{50} concentrations of the extract were similar for non-site-specific deoxyribose assay and site-specific deoxyribose assay such as 66 ± 20 μg ml^{-1} and 79 ± 17 μg ml^{-1} respectively [51]. The effect of ethyl acetate extract of *Teucrium polium* on 2-deoxy-D-ribose (dRib)-induced oxidative stress and apoptosis in erythroleukemic K562 cells was also evaluated. Treatment with ethyl acetate extract (25 and 50 mg/ml) reduced oxidative stress and apoptosis among the dRib-treated K562 cells. The results demonstrated that the antioxidant property of Ethyl acetate extract mainly results from increasing the level of cellular GSH by inducing the activity of c-GCS. Reports have found that the Ethyl acetate extract of *T. polium* prevents dRib-induced oxidative stress and apoptosis mostly through antioxidative mechanisms [52].

In a β-carotene linoleic acid model system, methanol extract, rutin, apigenin and 3',6-dimethoxyapigenin inhibited the

discoloration of beta-carotene with 25.8 ± 1.2, 26.7 ± 1.9, 27.4 ± 2.2 and 20.2 ± 2.2 mm mean zone of color retention respectively . These results correspond to their free radical scavenging activity of tested fractions. The methanol extract, rutin and apigenin exhibited inhibition of lipid peroxidation [48]. It was also found that the aqueous extract is an efficient scavenger of free oxygen radical [51].

In vivo antioxidant activity

Flavonoids that have been isolated from *T. polium* species include cirsimaritin, cirsilol, cirsilineol, 5-hydroxy-6,7,3',4'-tetramethoxyflavone, salvigenin, apigenin 5-galloylglucoside, apigenin-7-glucoside, vicenin-2- and luteolin-7-glucoside. The antioxidant potential of cirsimaritin and apigenin-7-glucoside has been indicated. Vicenin and luteolin-7-glucoside have shown the strongest antioxidant activity in *vitro* tests. Polyphenolic compounds have also shown strong antioxidant activity. The positive effects of these antioxidant components come from their ability to inhibit lipid peroxidation and chelate redox-active metals. Data obtained by DPPH, FRAP, and TBARS assays indicated that *T. polium* effectively inhibits oxidative stress *in vivo*. When tested by FRAP and TBARS, *T. polium* extract at a dose of 200 mg kg^{-1} per day exhibited no significant antioxidant activity in comparison to the control. It is proposed that the DPPH test is more sensitive than FRAP and TBARS tests for examination of the antioxidant capacity of *T. polium* [50]. The antioxidant activity of *T. polium* was also demonstrated in a recent *in vivo* study of rats. Rats were treated with a *T. polium* extract that showed significant antioxidant activity in the DPPH test compared to the positive control (α-tocopherol). The *T. polium* extract given to rats at doses of 50 and 100 mg/kg significantly increased the total antioxidant power (TAP) and decreased the thiobarbuteric acid reactive substances (TBARS) relative to the control [2].

Antiproliferative activity

The effects of *TP* extract on cell proliferation, cell cycle progression and cell death in H322 and A549 lung cell lines. Results showed that *TP* plant extract inhibits cell proliferation and deregulates cell cycle progression, *TP* plant extract causes a dramatic cell death in both cell lines in comparison with untreated cells [53]. The effects of aqueous extract of *Teucrium polium* on selected parameters in PC3 and DU145 prostate cancer cell lines was evaluated. Results showed that extract inhibits cell proliferation and provokes S cell cycle arrest and reduction of G0–G1 phase. TP plant extract also caused a dramatic decrease in cell invasion and motility abilities of PC3 and DU145 cancer cells in comparison with untreated cells. These changes are accompanied by a re-localization of the expression patterns of E-cadherin and catenins. The molecular pathway analysis of the TP plant extract revealed that it inhibits the phosphorylation of β-catenin, via Src dephosphorylation, and consequently converts its role from a transcriptional regulator to a cell–cell adhesion molecule. Therefore, plant extract has therapeutic promise in the treatment of human metastatic prostate cancer and other cancer diseases [55].

Hypotensive and cardio protective activity

The prevalence of cardiovascular diseases is very high and increases dramatically worldwide. Hypertension is a very important risk factor for development of other cardiovascular diseases such as myocardial infarction and heart failure. The impact of aqueous-ethanol extract of TP on blood pressure, heart rate and intraventricular pressure was investigated in rabbit. Treatment with 80 mg/kg of TP extract significantly depressed the mean arterial blood pressure (12.5%, $P< 0.05$). However, there was no significant decrease in the 20 or 40 mg/kg dose or normal saline treatment group. Moreover, the extract increased (dp/dt) max ($P<0.05$), maximum left ventricular pressure (LVP_{max}) ($P<0.05$) and decreased (dp/dt) min significantly ($P<0.05$), there was no meaningful effect on left ventricular end-diastolic pressure (LVEDP). Results demonstrated that the extract had no effect on the heart rate, but showed a positive inotropic on the heart and hypotensive effects. These data suggested that hypotensive effect may counterbalance by the inotropic effect of the extract [62].

Heptotoxicty

The use of herbal remedies can pose serious direct and indirect health risks. The plant *Teucrium polium* (family Lamiaceae), used worldwide in traditional and herbal medicine has been reported, in a few reports, to cause hepatotoxicity in humans. The acute and chronic toxicity of *Teucrium polium* L. a common folklore treatment for hyperglycemic conditions and various other ailments, was evaluated in mice using both an acute (24 h) and chronic (3 months) toxicity test using mice. Animals given a single oral dose of *T. polium* extract in the acute test had decreased loco-motor activity, compared with controls. Animals treated with *T. polium* extract in the chronic test did not gain body weight, developed a significant increase in the weight of the liver and kidneys and a significant reduction in weight of testes of the male mice, compared with the control group. In animals treated with *T. polium*, histopathological and biochemical studies revealed congestion and necrotic changes in the liver, a significant increase in ALT and AST levels in liver tissues, and a reduction in blood glucose levels, compared with the control. A significant increase in sperm abnormalities was also noticed in the male animals chronically treated with *T. polium*, compared with the control animals [42]. The effects of chronic treatment with small sub lethal doses (20 mg/kg and 50 mg/kg) of ethanolic extract of *Teucrium polium* were also investigated. Hematological and biochemical parameters of the blood, as well as sperm count, morphology and motility were normal after 6 weeks of herbal treatment. However, blood urea ($P < 0.05$) and cholesterol ($P < 0.005$) were significantly increased, with marked cytoplasmic vacuolation of the liver and kidney cells after chronic treatment with 50 mg/kg of the plant. These results demonstrate some histopathological effects of *T. polium* on the liver and kidney under long-term administration conditions the hypoglycemic effect that has been described for *T. polium* were found after short-term herbal administration, which is probably due to a transient effect on the homeostatic regulatory carbohydrate metabolism these reveals that the phytotoxic effect of the medicinal plant *T. polium* on the liver and kidney resulted in a rise in urea and cholesterol levels after prolonged herbal administration [43].

Acute cholestatic hepatitis

Three cases of acute hepatitis were reported after using *T. polium* for treating hyperlipidemia and hypoglycemia [59]. In

some instances, acute cholestatic hepatitis was seen in patients who had prolonged use of *Teucrium polium* as a hypolipidemic herbal remedy. Although the mechanism of *Teucrium polium* hepatotoxicity is unclear, teucrin A and several neoclerodane diterpenoids, present in the aerial parts of the plant, have been reported as the probable hepatotoxic precursors of this herb. In some instances, the liver injury has been associated with the presence of auto antibodies in the serum. A case of acute cholestatic hepatitis with transient appearance of antimitochondrial antibody was observed in a woman after the prolonged use of *Teucrium polium* as an herbal remedy for symptoms of diabetes mellitus. Another report revealed that massive hepatocyte necrosis predominantly in the centrilobular areas of the liver also observed in the patients with acute liver failure after the consumption of *Teucrium polium* [46].

CONCLUSION

Teucrium polium L. is a medicinal plant; each part of the plant was used for the treatment of various diseases. This versatile medicinal plant is the unique source of various types of chemical compounds, which are responsible of the various activities of the plant. It has been experimentally proved that *Teucrium polium* L. possess antioxidant, antimicrobial, anticancer, diuretic, wound-healing, antiviral, antidiabetic, hepatoprotective, mosquito larvicidal, anti-inflammatory and analgesic, cardio protective activity, and antinociceptive properties. But in some cases, its prolonged use causes hepatotoxicity. Considering the temporal relationship between the increase of the dose and the occurrence of toxicity, further research is required to evaluate the potential value of *Teucrium polium* for the management of hyperlipidemia and establish safety profiles of *Teucrium polium* products.

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